

(表紙記載例)

学 位 論 文

学位論文名： Control status of atherosclerotic cardiovascular risk
factors among Japanese high-risk subjects: Analyses of a Japanese
Health Check Database from 2008 through 2011

(本邦における動脈硬化性疾患高リスク者の管理状況について: 20
08年から2011年の健診データによる検討)

※論文名が英文の場合は、日本語訳を () 内に付記すること。

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Control Status of Atherosclerotic Cardiovascular Risk Factors Among Japanese High-Risk Subjects:

Analyses of a Japanese Health Check Database from 2008 to 2011

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Aims: Several guidelines propose target levels (TLs) of atherosclerotic risk factors (ARFs) to reduce atherosclerotic cardiovascular diseases; however, few data are available regarding the attainment statuses of TLs in Japan. In this study, utilizing the data obtained from the annual "Specific Health Check and Guidance in Japan" conducted from 2008 to 2011 (approximately 280,000 subjects each year), we determined TL attainments of ARFs in cardiovascular high-risk subjects.

Methods: Those who had suffered from cerebrovascular disease (pCVD) or coronary heart disease (pCHD) or were receiving diabetes mellitus treatment (DM) were selected, and the rates of subjects that attained TLs of blood pressure (BP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs) and glycated hemoglobin (HbA1c) were analyzed.

Results: Approximately 70% of pCVD or pCHD and 35% of subjects with DM attained TLs of BP. With regard to HbA1c, >90% of pCVD or pCHD and approximately 50% of subjects with DM attained TLs. With regard to LDL-C, <25% of pCHD females and approximately 35% of pCHD males and 50%–55% of subjects with pCVD or DM attained TLs. The TL-attainment rates of HDL-C and TGs were approximately 90% and 75%, respectively, for the three diseases. Analyses of time course changes in their attainment statuses revealed that the attainment rates of BP and LDL-C significantly improved in all the diseases.

Conclusions: TL-attainment rates of BP and LDL-C were not as high as those for HDL-C, TGs, and HbA1c; however, they both showed highly significant improvements during the study period.

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Key words: Atherosclerotic risk factors, Control status, Cardiovascular high-risk patient, Japanese

Abbreviations: TL: target level, ARF: atherosclerotic cardiovascular risk factor, pCVD: previously suffered from cerebrovascular disease, pCHD: previously suffered from coronary heart disease, DM: diabetes under treatment, BP: blood pressure, HbA1c: glycated hemoglobin, NGSP: national glycohemoglobin standardization program, TG: triglyceride, HDL-C: HDL-cholesterol, LDL-C: LDL-cholesterol, SHCG: Specific Health Check and Guidance in Japan, JDS: Japan Diabetes Society, JDDM: The Japan Diabetes Clinical Data Management Group

Introduction

Mortality rate due to atherosclerotic cardiovascu-

lar disease in Japan is almost as high as that for malignant diseases. To reduce the incidence of atherosclerotic cardiovascular diseases, the Japanese Society for

Hypertension¹⁾, the Japan Atherosclerosis Society²⁾, and the Japan Diabetes Society (JDS)³⁾ define the target levels (TLs) of cardiovascular atherosclerotic risk factors (ARFs) depending on the clinical status of each individual. Among the clinical status, a past history of coronary heart disease (pCHD), a past history of cerebrovascular disease (pCVD), and current diabetes mellitus are classified as very high or high risk of atherosclerotic diseases. Furthermore, intensive treatment of ARFs, such as high blood pressure (BP), dyslipidemia, and diabetes, is recommended to subjects with such clinical statuses. TLs of BP have been set to <140/90 mmHg for patients with pCHD and pCVD and <130/80 mmHg for diabetic patients¹⁾. The glycated hemoglobin (HbA1c) level measured with the national glycohemoglobin standardization program (NGSP) has been set to <7.0% for all subjects to reduce the occurrence of diabetes-associated complications³⁾. With regard to lipid control, TLs for HDL cholesterol (HDL-C), and triglyceride (TG) have been set to ≥ 40 mg/dL and <150 mg/dL, respectively, for the three diseases, and TL for LDL cholesterol (LDL-C) has been set to <100 mg/dL for pCHD and <120 mg/dL for diabetes mellitus and pCVD²⁾.

In addition to these recommendations for TLs agreed upon by Japanese medical societies, the Japanese government initiated the nationwide annual "Specific Health Check and Guidance in Japan (SHCG)" in 2008⁴⁻⁶⁾. This project aimed to identify those who are under or at a high-risk state for metabolic syndrome and subsequently to instruct them regarding how to improve their lifestyle, thereby reducing the prevalence of metabolic syndrome and atherosclerotic cardiovascular diseases^{7, 8)} in the future. This health check is administratively mandatory for all people aged between 40 and 74 years, and public medical insurances are responsible for performing this health check and guidance for their insurees and insurees' dependents.

Despite the aforementioned TLs recommended by several societies, few data are available that show the current attainment status of TLs in those who are at high risk of atherosclerotic cardiovascular diseases. Furthermore, the recent transitional changes in TL attainment are absent after the initiation of SHCG.

Aim

In this study, utilizing SHCG data between 2008 and 2011, we analyzed the rates of TL attainment of ARFs in patients with pCHD, pCVD, and DM and examined the recent tendencies in their attainment status.

Methods

Study Population and Design

This study utilized data of the nationwide SHCG annually conducted by the insurers for community residents and employees from 2008 to 2011. We utilized data collected from 16 prefectures (Hokkaido, Miyagi, Ibaraki, Tochigi, Saitama, Chiba, Fukui, Ishikawa, Nagano, Gifu, Hyogo, Tokushima, Saga, Nagasaki, Kumamoto, and Okinawa) whose data during 2008–2011 had already been fixed and available by the end of 2014. All data obtained from 15 prefectures other than Okinawa were supplied from the local municipalities as insurers of "National Health Insurance." The data obtained from Okinawa prefecture included not only the data from local municipalities but also those obtained from "Japan Health Insurance Association," one of the insurers of employees' insurance. The numbers of the participants of each prefecture in each year are listed in **Table 1**. Individual data were sent to and verified by an independent data center, the NPO Japan Clinical Support Unit (Tokyo, Japan). All participants remained anonymous, and the study was conducted according to the Japanese privacy protection law and ethical guidelines for epidemiological studies published by the Ministry of Education, Science, and Culture and the Ministry of Health, Labour and Welfare.

SHCG has been described previously⁴⁻⁶⁾. In this system, participants answer a self-administered questionnaire that covers medical history and current lifestyles (smoking status, alcohol intake, exercise habits, eating habits, and sleep condition). The body height, body weight, waist circumference, and BP are measured by trained medical staff, and blood and urine samples are collected for the measurement of clinical chemical data. All blood analyses are conducted at a local, rather than a central, laboratory. Although the methods for blood analyses are not calibrated between laboratories, analyses are performed according to the Japan Society of Clinical Chemistry-recommended methods for laboratory tests, which have been widely adopted by laboratories across Japan^{9, 10)}.

From the abovementioned cohort, we excluded those whose sex data were unavailable and those whose

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Table 1. Number of participants from each prefecture for each year

Prefecture	Year			
	2008	2009	2010	2011
Hokkaido	37,577	39,559	39,002	38,220
Miyagi	17,892	17,212	1,208	1,232
Ibaraki	39,968	42,578	45,023	46,318
Tochigi	5,851	6,113	6,193	6,420
Saitama	3,427	3,240	3,736	3,745
Chiba	4,199	4,227	4,861	4,933
Fukui	1,421	1,437	1,432	1,492
Ishikawa	6,620	8,686	9,340	10,113
Nagano	15,139	16,970	17,085	16,537
Gifu	9,984	10,223	10,189	9,764
Hyogo	7,513	9,007	9,180	9,575
Tokushima	7,061	8,703	9,027	5,829
Saga	2,908	2,702	2,846	2,699
Nagasaki	16,939	18,166	18,644	14,977
Kumamoto	23,385	23,087	23,856	24,883
Okinawa	69,561	82,847	89,862	92,976
Total	269,445	294,757	291,484	289,713

Table 2. Target levels of each atherosclerotic cardiovascular risk factor in each disease in Japan

The values are indicated in references #1, 2 and 3

Risk factor	pCHD	pCVD	DM
BP (mmHg)	< 140/90	< 140/90	< 130/80
HbA1c (%)	< 7.0	< 7.0	< 7.0
LDL-C (mg/dL)	< 100	< 120	< 120
HDL-C (mg/dL)	≥ 40	≥ 40	≥ 40
TG (mg/dL)	< 150	< 150	< 150

responses to each questionnaire were missing. We used the data of those who had a past history of cerebrovascular or coronary heart disease or those who used medication for diabetes mellitus. Number and rates of subjects who attained or did not attain TLs of each ARF (i.e., BP, HbA1c, LDL-C, HDL-C, and TG) were analyzed in each year for each disease. HbA1c level measured as HbA1c (JDS) from 2008 to 2011 in this cohort was converted to HbA1c (NGSP) using the following equation: HbA1c (NGSP) (%) = HbA1c (JDS) (%) + 0.4%¹¹⁾. The subjects with missing values of these ARFs were excluded from the analyses. TLs of each ARF in each disease, recommended by several Japanese societies, are listed in **Table 2**.

Statistical Analysis

Data were analyzed separately by sex. The trends of the prevalence of each disease and those of TL

attainment status for each ARF in each disease over time were analyzed by the Cochran–Armitage test using Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan). Linear regression analyses were performed to examine whether the year-by-year changes in the TL-attainment rates of risk factors were significant or not after adjustment for other atherosclerotic risk factors, which were available in SHCG database and medication for each risk factor. Continuous values were utilized for year, age, body mass index, estimated glomerular filtration rate, uric acid, HbA1c, TG, HDL-C, and LDL-C. With regard to other variables and dependent variables, ordinal values, which are shown in **Table 3**, were used. SPSS for Windows statistical package (versions 21.0 & 22.0; SPSS, Chicago, IL, USA) was used for the analyses. *P*-values < 0.05 were considered to be statistically significant. The odd ratios indicate the proba-

Table 3. Ordinal values utilized for the logistic regression analyses

Variables	Ordinal Value	
	1	2
Dependent variables	Attained TL	Did not attain TL
Smoking	Smoker	Non Smoker
pCVD	With pCVD	Without pCVD
pCHD	With pCHD	Without pCHD
Medication	Taking Medicine	Not taking Medicine

Table 4. Prevalence of each disease for 2008–2011

Year		2008		2009		2010		2011	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
Percentage of each disease (%)	pCHD	7.79	5.06	7.29	4.47	6.87	4.14	6.85	4.06
	pCVD	6.14	3.90	4.63	2.49	4.58	2.46	4.38	2.34
	DM	7.39	4.21	7.68	4.42	8.06	4.51	8.65	4.74

bilities for the TL nonattainment risk increase when the independent variables increase by one or one unit.

Results

Numbers of Available Data for the Analyses and the Prevalence Rates of High-Risk Diseases and Their Trends for 2008–2011

Table 4 and Supplementary Table 1 show the total numbers of participants in this cohort of both sexes in each year, numbers of available data of each questionnaire, and prevalence rates of each disease in each sex in each year. For each year, approximately 280,000 participants were included in the analyses, and 42%–43% of the participants in all years were male. The prevalence of pCHD was 7.79% for males and 5.06% for females in 2008, and it significantly decreased year-by-year to 6.85% and 4.06% in 2011 for males ($p < 0.001$) and females ($p < 0.001$), respectively. The prevalence of pCVD gradually and significantly decreased from 6.14% to 4.38% for males ($p < 0.001$) and from 3.90% to 2.34% for females ($p < 0.001$). In contrast, the prevalence of diabetes mellitus treated with medication increased from 7.39% to 8.65% for males ($p < 0.001$) and from 4.21% to 4.74% for females ($p < 0.001$) from 2008 to 2011. With regard to the rates of the available data for ARFs, they reached approximately 100% in all the diseases in both sexes over the study period (Supplementary Table 2). The average ages of subjects with pCVD, pCHD, and DM in each year in each sex are shown in

Supplementary Table 3, and the percentages of those who had been taking medicine for risk factors are shown in Supplementary Table 4.

TL Achievement Rate of ARFs in Each Disease

The rates of subjects who attained TLs of each ARF in each disease in each year are shown in Table 5, and the results of logistic regression analyses of the TL attainment of those subjects are shown in Table 6. The rates of TL attainment of BP were approximately 60%–70% in subjects with pCVD and pCHD, whereas the rates were only approximately 35% in subjects with DM whose BP TL had been set to be stricter than those of pCVD and pCHD. Surprisingly, in all the diseases in both sexes, the rates of attainment of BP TLs increased gradually and significantly by more than 5% from 2008 to 2011; the p values of these trends were $< 1.0 \times 10^{-11}$. In addition, logistic regression analyses revealed that the year-by-year improvements in BP control in all three diseases in both sexes were highly significant even after adjustment for other risk factors and hypertension medication. Furthermore, the logistic analyses revealed that the odds ratios of hypertension medication were lower than one in all the diseases, indicating that the BP in subjects who had received hypertension medication was less controlled compared with that in subjects who had not received the medication.

Although the current TL of BP for pCHD is $< 140/90$ mmHg, the TL before 2013 was set to $< 130/80$ mmHg. As shown in Supplementary Table 5,

Table 5. Target level attainment rates for atherosclerotic cardiovascular risk factor in each disease in each sex (%)

P values of the time course change analysis of the attainment rate using the Cochran-Armitage test are also indicated.

A. BP						
Year		2008	2009	2010	2011	<i>p</i> value
pCVD	Male	60.4	64.4	66.5	66.4	<0.001
	Female	65.4	69.4	71.3	72.2	<0.001
pCHD	Male	66.1	69.3	71.3	71.6	<0.001
	Female	68.3	71.3	73.2	75.3	<0.001
DM	Male	32.1	34.4	36.0	37.1	<0.001
	Female	33.5	35.3	37.7	39.2	<0.001
B. LDL-C						
Year		2008	2009	2010	2011	<i>p</i> value
pCVD	Male	55.2	57.8	60.5	61.3	<0.001
	Female	45.5	47.1	50.0	51.3	<0.001
pCHD	Male	31.6	34.2	37.5	38.2	<0.001
	Female	20.3	22.8	25.4	27.2	<0.001
DM	Male	59.0	60.1	62.9	64.1	<0.001
	Female	48.0	50.2	53.5	56.0	<0.001
C. HDL-C						
Year		2008	2009	2010	2011	<i>p</i> value
pCVD	Male	87.7	87.8	87.6	87.0	0.23
	Female	96.1	95.8	96.2	96.6	0.22
pCHD	Male	87.5	87.9	88.0	87.6	0.83
	Female	95.6	96.2	96.0	96.3	0.07
DM	Male	86.6	86.9	86.8	86.4	0.56
	Female	94.7	94.6	94.9	95.1	0.25
D. TG						
Year		2008	2009	2010	2011	<i>p</i> value
pCVD	Male	70.9	72.2	72.3	73.6	<0.01
	Female	76.5	79.4	78.9	79.3	<0.01
pCHD	Male	71.8	73.7	73.0	72.7	0.50
	Female	77.7	79.8	79.6	79.4	<0.05
DM	Male	69.3	69.8	69.1	70.6	0.09
	Female	73.3	73.1	74.0	74.0	0.21
E. HbA1c						
Year		2008	2009	2010	2011	<i>p</i> value
pCVD	Male	92.9	92.8	91.5	91.2	<0.001
	Female	95.6	94.9	95.0	94.6	0.07
pCHD	Male	91.0	92.2	91.5	92.0	0.17
	Female	94.1	94.7	94.8	95.0	<0.05
DM	Male	55.3	54.0	53.0	55.9	0.42
	Female	54.3	53.8	53.0	55.5	0.23

Table 6. Logistic regression analyses of the TL attainment of atherosclerotic cardiovascular risk factors

The independent effects of year, medication and other risk factors on the attainment for the TLs of atherosclerotic cardiovascular risk factors were evaluated using logistic regression analyses, using SPSS (Chicago, IL). *P* values and odds ratios (OR) are indicated. DrugBP: medication for hypertension, DrugLP: medication for dyslipidemia, DrugBS: medication for glycemic control.

A. BP															
		Year	Age	BMI	eGFR	Smoking	UA	HbA1c	TG	HDL-C	LDL-C	pCVD	pCHD	DrugBP	
pCVD	Male	<i>p</i> value	<0.001	<0.05	<0.001	0.779	0.347	<0.01	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001	
		OR	0.925	1.007	1.048	NA	NA	1.044	1.091	1.001	1.012	1.003	1.125	0.611	
	Female	<i>p</i> value	<0.001	<0.001	<0.001	0.051	0.784	0.391	<0.01	<0.01	<0.001	<0.001	0.682	<0.001	
		OR	0.901	1.022	1.062	NA	NA	NA	1.101	1.001	1.007	1.004	NA	0.576	
pCHD	Male	<i>p</i> value	<0.001	<0.001	<0.001	0.636	0.280	<0.001	0.084	<0.001	<0.001	<0.05	<0.001	<0.001	
		OR	0.908	1.016	1.058	NA	NA	1.042	NA	1.002	1.012	1.004	0.904	0.590	
	Female	<i>p</i> value	<0.001	<0.001	<0.001	<0.001	0.167	0.219	<0.01	<0.001	<0.001	<0.001	0.405	<0.001	
		OR	0.889	1.024	1.050	1.004	NA	NA	1.085	1.001	1.005	1.005	NA	0.475	
DM	Male	<i>p</i> value	<0.001	<0.001	<0.001	<0.001	<0.001	0.355	<0.01	<0.001	<0.001	0.071	<0.001	<0.001	
		OR	0.903	1.009	1.087	1.003	1.242	NA	1.042	1.002	1.011	1.003	NA	1.277	0.433
	Female	<i>p</i> value	<0.001	<0.001	<0.001	<0.001	<0.001	0.352	<0.001	<0.001	<0.001	<0.001	<0.05	<0.01	<0.001
		OR	0.893	1.029	1.077	1.004	1.301	NA	1.060	1.001	1.006	1.005	0.851	1.195	0.417
B. LDL-C															
		Year	Age	BMI	eGFR	Smoking	UA	SBP	HbA1c	pCVD	pCHD	DrugLP			
pCVD	Male	<i>p</i> value	<0.001	<0.001	<0.001	0.268	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
		OR	0.918	0.987	1.031	NA	1.105	1.083	1.003	1.113		1.439	1.570		
	Female	<i>p</i> value	<0.001	<0.001	<0.001	0.569	0.900	<0.01	<0.001	<0.05	<0.01	<0.01	<0.001	<0.001	
		OR	0.927	NA	1.026	NA	NA	1.061	1.008	1.078		1.216	2.422		
pCHD	Male	<i>p</i> value	<0.001	<0.001	<0.001	0.122	0.095	<0.001	<0.001	<0.001	0.109	<0.001	<0.001	<0.001	
		OR	0.923	0.986	1.042	NA	NA	1.058	1.004	1.089	NA		1.883		
	Female	<i>p</i> value	<0.001	<0.001	<0.001	0.623	0.174	0.146	<0.001	0.604	0.073	<0.001	<0.001	<0.001	
		OR	0.900	NA	1.022	NA	NA	NA	1.007	NA	NA		2.414		
DM	Male	<i>p</i> value	<0.001	<0.001	<0.001	<0.001	0.058	<0.001	<0.01	<0.001	0.061	<0.001	<0.001	<0.001	
		OR	0.940	0.991	1.038	0.997	NA	1.039	1.003	1.222	NA	1.426	1.332		
	Female	<i>p</i> value	<0.001	<0.001	0.140	0.197	0.188	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	
		OR	0.909	0.980	NA	NA	NA	1.114	1.007	1.157	1.232	1.356	1.873		

C. HDL-C

	Year	Age	BMI	eGFR	Smoking	UA	SBP	HbA1c	pCVD	pCHD	DrugLP
pCVD	Male	0.136	<0.001	<0.001	<0.001	<0.05	<0.001	<0.001		0.287	0.549
	OR	NA	1.094	0.989	0.663	1.036	0.993	1.282		NA	NA
	Female	0.551	<0.05	0.148	0.403	<0.001	0.371	<0.001		0.753	0.858
	OR	NA	1.044	NA	NA	1.360	NA	1.436		NA	NA
pCHD	Male	0.867	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001	0.467		0.112
	OR	NA	1.111	0.986	0.560	1.084	0.992	1.242	NA		NA
	Female	0.759	<0.001	<0.05	0.124	<0.001	0.971	<0.001	0.822		<0.01
	OR	NA	1.046	0.993	NA	1.266	NA	1.385	NA		1.324
DM	Male	0.264	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	OR	NA	1.078	0.987	0.626	1.066	0.992	1.125	0.750	0.807	1.178
	Female	0.175	<0.001	<0.05	<0.05	<0.001	0.430	<0.001	0.354	<0.01	<0.01
	OR	NA	1.034	0.996	0.755	1.359	NA	1.154	NA	0.744	1.249

D. TG

	Year	Age	BMI	eGFR	Smoking	UA	SBP	HbA1c	pCVD	pCHD	DrugLP
pCVD	Male	<0.05	<0.001	<0.01	<0.001	<0.001	<0.01	<0.001		<0.05	<0.001
	OR	0.959	1.103	0.996	0.668	1.202	1.004	1.329		1.115	0.738
	Female	<0.05	<0.001	0.080	<0.001	<0.001	<0.001	<0.001		<0.01	<0.01
	OR	0.944	1.058	NA	0.666	1.331	1.006	1.494		0.822	0.845
pCHD	Male	0.055	<0.001	<0.05	<0.001	<0.001	<0.001	<0.001	0.108		<0.001
	OR	NA	1.106	0.997	0.606	1.225	1.009	1.246	NA		0.787
	Female	0.532	<0.05	0.397	<0.001	<0.001	<0.001	<0.001	<0.05		<0.001
	OR	NA	1.065	NA	0.619	1.344	1.007	1.378	0.849		0.833
DM	Male	0.246	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.714	<0.001	<0.001
	OR	NA	1.089	0.997	0.679	1.206	1.008	1.278	NA	1.177	0.685
	Female	0.724	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	0.100	0.199	<0.001
	OR	NA	1.050	0.997	0.724	1.327	1.004	1.343	NA	NA	0.785

E. HbA1c

	Year	Age	BMI	eGFR	Smoking	UA	SBP	TG	HDL-C	LDL-C	pCVD	pCHD	DrugBS
pCVD	Male	0.683	<0.001	<0.05	<0.01	<0.001	<0.01	<0.001	<0.05	<0.001		0.619	<0.001
	OR	NA	1.072	1.005	0.729	0.807	1.008	1.003	0.994	1.009		NA	0.042
	Female	0.429	<0.001	<0.001	0.401	<0.05	<0.01	<0.001	<0.05	<0.01		0.845	<0.001
	OR	NA	1.060	1.014	NA	0.887	1.010	1.007	0.989	1.005		NA	0.025
pCHD	Male	0.632	<0.001	<0.001	<0.05	<0.001	<0.01	<0.001	<0.05	<0.001	0.579		<0.001
	OR	NA	1.061	1.006	0.836	0.815	1.006	1.003	0.994	1.008	NA		0.036
	Female	<0.05	<0.001	<0.001	<0.05	<0.05	<0.001	<0.001	<0.001	<0.001	0.210		<0.001
	OR	0.921	1.062	1.009	1.557	0.918	1.010	1.003	0.985	1.006	NA		0.019
DM	Male	0.233	<0.001	<0.001	<0.01	<0.001	<0.001	<0.001	<0.01	<0.001	<0.05	0.153	
	OR	NA	1.023	1.004	0.900	0.806	1.003	1.002	0.997	1.008	1.121	NA	
	Female	0.103	<0.001	<0.001	0.160	<0.001	<0.001	<0.001	0.117	<0.001	<0.05	0.114	
	OR	NA	1.021	1.007	NA	0.845	1.005	1.004	NA	1.006	1.170	NA	

the analyses utilizing TL of BP <130/80 in pCHD also revealed highly significant year-by-year improvements in both sexes.

The rates of TL attainment of LDL-C in subjects with pCVD and DM were approximately 60% and 50% for males and females, respectively. In contrast, those in pCHD were comparatively low, only approximately 35% for males and 24% for females. However, it is noteworthy that the rates of TL attainment of LDL-C increased gradually and significantly by more than 5% from 2008 to 2011 in all the diseases in both sexes; the *p* values of these trends were less than 1.0×10^{-7} with Cochran–Armitage test, and logistic regression analyses revealed significant year-by-year improvements in LDL-C control in all the diseases, even after adjustment for other risk factors and medication for dyslipidemia. In addition, the logistic regression analyses revealed that the odds ratios of medication for dyslipidemia were higher than 1, suggesting that the control of LDL-C in the analyzed subjects was better in subjects who had been taking medicine for dyslipidemia than in those who had not.

In all the diseases, the rates of TL attainment of HDL-C for males and females were approximately 87% and 95%, respectively; the attainment rates were higher for females than for males in all diseases. No significant changes were observed over the study period in all diseases in both sexes.

Regarding TG levels, the rates of TL attainment were approximately 70%–80% in all the diseases in both sexes. In subjects with pCVD and female subjects with pCHD, the attainment rates increased significantly during the study period, and this significant improvement was observed in subjects with pCVD after adjustment for other factors; however, the *p* values were much greater than those found in the analyses of BP and LDL-C. The logistic regression analyses revealed that those who received dyslipidemia medication did not attain better control than those who did not take medication, a contrary result found in LDL-C control.

The rates of TL attainment of HbA1c reached >90% in subjects with pCVD and pCHD of both sexes, whereas those rates were only approximately 54% in subjects with DM. Statistically significant changes in the attainment rate of HbA1c TL were observed in male subjects with pCVD and female subjects with pCHD by Cochran–Armitage test. This significance remained only in female subjects with pCHD after adjustment for other factors; however, the *p* value was much greater than those found in the analyses of BP and LDL-C. Furthermore, the logistic regression analyses revealed that the odds ratios of

medication for glycemic control for subjects with pCVD and pCHD were <1, suggesting that those who were being treated with medication for glycemic control attained poorer glycemic control than those who were not being administered with antidiabetic agents.

Discussion

Adequate control of ARFs has been known to be crucial for the prevention of atherosclerotic cardiovascular diseases, especially in high-risk subjects. Several studies surveying the control status of lipids and BP in Japanese patients have been reported^{12–15}; however, these studies targeted only those who had been taking medications for lipids or BP, suggesting that the results of these studies do not reflect the overall control status including those who are not on medication. The Japan Diabetes Clinical Data Management (JDDM) Group has been analyzing the status of glycemic control in diabetic patients since 2002¹⁶; however, at present, no such data have been available in subjects with pCHD and pCVD in Japan. The Ministry of Health, Labour and Welfare of the Japanese government annually performs National Health and Nutrition Examination Survey by randomly selecting approximately 6,000–10,000 subjects from the general Japanese population and releases the data on its homepage¹⁷; however, understandably, no data are available on the control status in those who are at high risk of atherosclerotic diseases. Thus, in this study, utilizing the data obtained from the nationwide SHCG conducted from 2008 to 2011, we systematically analyzed the control status of BP, lipids, and HbA1c levels in those who had ever experienced CVD or coronary heart disease and those who were on medication for diabetes.

One of the major findings of this study was that the rates of TL attainment of BP and LDL-C were highly significantly improved year-by-year during the study period in all the diseases in both sexes. In contrast, the TL-attainment rates of HDL-C did not change over the study period in all the diseases. Regarding TG TL, the attainment rates improved significantly in subjects with pCVD, although the improvements were less than those found for BP and LDL-C analyses. Several explanations would be plausible for these differences in the improvement of the control status among ARFs. One such explanation is that the TL-attainment rates of HDL-C are higher than those of other ARFs, reaching >90% throughout the study period in all the diseases in both sexes, which led to less apparent improvement in HDL-C levels. The next possible explanation is that the controls of LDL-C and BP are easier than that of HDL-C;

there are several medications that attain the reduction of LDL-C and BP with comparative ease, whereas strategies that increase HDL-C are few and not prevalent. In addition, physicians give more attention to the control of LDL-C and BP than that of HDL-C. With regard to the use of antihyperlipidemic medications, ezetimibe became available in 2007 in Japan, in addition to that a class of statins that effectively reduces cholesterol levels has become popular after around 2008 in Japan. A previous study¹⁴⁾ has shown that the additional prescription of ezetimibe to statin resulted in higher TL-attainment rates of LDL-C. With regard to antihypertensive medications, physicians can choose from various kinds of agents of each class medication, such as calcium channel blocker, and angiotensin II receptor blocker. The other plausible reason is that this nationwide project itself, which aimed to reduce metabolic syndrome, has evoked attention to its prevention not only in the general population but also in physicians. In this case, more attention could have been given to lifestyle modification by the general population, and physicians could have better recognized the guidelines agreed upon by medical societies and the importance of stricter control of ARFs¹⁸⁾. Further observation of this cohort would determine whether this nationwide project exerts beneficial effects on the control of ARFs. Furthermore, if this nationwide project resulted in beneficial effects on ARF control, a similar health check system can be warranted in other countries because metabolic syndrome and cardiovascular diseases threaten human health worldwide.

With regard to glycemic control, we could find improvement only in female subjects with pCVD, and the improvement found in female subjects with pCVD was less compared with those found for BP and LDL-C. One possible explanation for this tendency is that several randomized controlled trials¹⁹⁻²¹⁾, which were published in 2008 and 2009, had shown that the intensive glycemic control, which led higher incidence of hypoglycemia, did not reduce the cardiovascular events, and one study showed that intensive treatment resulted in higher mortality rate than conventional glycemic control. Thus, physicians may have sought to avoid hypoglycemia as an unintended side effect of the treatment²²⁾, resulting in no improvement in TL attainments in HbA1c.

Another notable finding in this study is that the percentage of subjects who had pCVD and pCHD decreased, whereas the percentage of diabetic subjects on medication increased during the study period. Concordant with this observation, according to the JDDM study, the percentage of diabetic patients who

had been prescribed diabetic medications increased between 2008 and 2012²³⁾. Several reasons would be plausible for this increase; one of them is that the number of diabetic patients in Japan keeps increasing year-by-year, as shown by the Ministry of Health, Labour and Welfare of Japan. The next possible reason is that the dipeptidyl peptidase-4 inhibitors, which can be administered safely without inducing hypoglycemia when prescribed alone and also known to be more effective in Japanese than Caucasian patients²⁴⁾, have become available and been widely used in Japan since 2008, resulting in the increased medication rate in diabetic patients.

Another interesting finding obtained in this study was the effects of medication for each risk factor. Medication for dyslipidemia provided a better control of LDL-C, whereas it did not for TG. Medication for hypertension as well as that for glycemic control did not provide a good control of BP and HbA1c, respectively. Therefore, physicians may need to reconsider the strategies they use for the treatment of risk factors for atherosclerotic diseases to reduce the incidence.

There are several limitations of this study. First, the data on past histories of coronary heart disease and CVD and diabetes on medication were obtained from self-administered questionnaires. However, the responses were considered to be accurate as these diseases are well recognized among the general Japanese population. Furthermore, when the participants were uncertain about how to answer the question, they received assistance from trained medical staff. Thus, mistakes among the answers are assumed to be few. Second, the present study included few salaried workers whose lifestyles may be quite different from those covered by "National Health Insurance." However, because the present study was comparatively large scale, the results of the year-by-year changes in each risk factor should reflect the overall tendency of the Japanese population. Third, the attainment rates obtained in this study may be higher than those in the general Japanese population. Although the SHCG is administratively mandatory for those who are covered by "National Health Insurance," it is practically voluntary for them because there is no legal force even if they do not take the check-up; thus only approximately 40% of the target subjects under "National Health Insurance" took the SHCG. The percentage of the insureds of "Japan Health Insurance Association" who took SHCG also reached only approximately 30%–40%. It is likely that those who do not take the SHCG pay less attention to their health than those who take it. Fourth, although the standardization of

blood analyses had been recommended by the Japan Accreditation Board in 2005⁹⁾ and the recommended methods for SHCG had been shown by the Ministry of Health, Labour and Welfare of Japan¹⁰⁾, the methods for blood analyses, which are performed according to the Japan Society of Clinical Chemistry-recommended methods in each laboratory, are not actually calibrated between laboratories. To minimize these problems, we chose only 16 prefectures whose data from 2008 to 2011 were available; however, we could not eliminate the bias caused by the lack of calibration between laboratories. Fifth, full adjustment for background factors is not possible for this study. Although we included available atherosclerotic risk factors as much as possible for the logistic regression analyses, several risk factors such as family history are not included in the SHCG database.

In summary, by analyzing the data of SHCG performed between 2008 and 2011, we found that the attainment rates of TLs of BP and LDL-C improved greatly among the subjects of this study, and the number of patients with pCHD and pCVD decreased during the period between 2008 and 2011. Although the observation period of the present study was comparatively short, we believe that enforcement of the SHCG, the first health check system initiated by the Japanese government, may have resulted in these improvements.

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None of the authors have any conflict of interest.

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Supplementary Table 1. Number of available data for the analyses, and number of subjects in each disease for 2008–2011

Year		2008		2009		2010		2011	
Total no. of subjects		269,445		294,757		291,484		289,713	
Total no. of subjects with available sex data		269,445		294,757		291,483		289,712	
No. of subjects		Male	Female	Male	Female	Male	Female	Male	Female
		113,618	155,827	126,400	168,357	126,326	165,157	126,372	163,340
No. of subjects with available data for each questionnaire	pCHD	87,144	121,241	104,214	141,499	110,183	144,796	112,588	146,235
	pCVD	87,404	121,812	105,148	142,835	111,216	145,962	112,504	146,036
	DM	108,681	148,976	121,418	162,161	121,659	159,348	122,065	157,803
No. of each disease	pCHD	6,785	6,138	7,597	6,331	7,567	6,000	7,709	5,931
	pCVD	5,366	4,750	4,864	3,560	5,091	3,595	4,931	3,412
	DM	8,035	6,269	9,325	7,160	9,810	7,180	10,563	7,483

Supplementary Table 2. Numbers and rates of available risk factor data for each disease, for each year**A. pCHD**

Year		2008		2009		2010		2011	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects with pCHD		6785	6138	7597	6331	7567	6000	7709	5931
No. (%) of available data on each risk factor	BP	6784 (100.0)	6134 (99.9)	7594 (100.0)	6330 (100.0)	7566 (100.0)	5998 (100.0)	7706 (100.0)	5928 (99.9)
	HbA1c	6678 (98.4)	6035 (98.3)	7469 (98.3)	6169 (97.4)	7434 (98.2)	5864 (97.7)	7580 (98.3)	5801 (97.8)
	LDL-C	6782 (100.0)	6138 (100.0)	7595 (100.0)	6330 (100.0)	7564 (100.0)	6000 (100.0)	7709 (100.0)	5929 (100.0)
	HDL-C	6782 (100.0)	6138 (100.0)	7597 (100.0)	6331 (100.0)	7566 (100.0)	6000 (100.0)	7707 (100.0)	5931 (100.0)
	TG	6784 (100.0)	6138 (100.0)	7596 (100.0)	6331 (100.0)	7567 (100.0)	6000 (100.0)	7707 (100.0)	5930 (100.0)

B. pCVD

Year		2008		2009		2010		2011	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects with pCVD		5366	4750	4864	3560	5091	3595	4931	3412
No. (%) of available data on each risk factor	BP	5362 (99.9)	4747 (99.9)	4862 (100.0)	3559 (100.0)	5089 (100.0)	3595 (100.0)	4929 (100.0)	3411 (100.0)
	HbA1c	5048 (94.1)	4327 (91.1)	4814 (99.0)	3511 (98.6)	5039 (99.0)	3551 (98.8)	4879 (98.9)	3377 (99.0)
	LDL-C	5365 (100.0)	4747 (99.9)	4864 (100.0)	3557 (99.9)	5089 (100.0)	3595 (100.0)	4931 (100.0)	3412 (100.0)
	HDL-C	5365 (100.0)	4750 (100.0)	4864 (100.0)	3560 (100.0)	5091 (100.0)	3595 (100.0)	4931 (100.0)	3412 (100.0)
	TG	5364 (100.0)	4750 (100.0)	4863 (100.0)	3560 (100.0)	5091 (100.0)	3595 (100.0)	4930 (100.0)	3412 (100.0)

C. DM

Year		2008		2009		2010		2011	
Sex		Male	Female	Male	Female	Male	Female	Male	Female
No. of subjects with DM		8035	6269	9325	7160	9810	7180	10563	7483
No. (%) of available data on each risk factor	BP	8028 (99.9)	6262 (99.9)	9320 (99.9)	7156 (99.9)	9805 (99.9)	7174 (99.9)	10560 (100.0)	7480 (100.0)
	HbA1c	7932 (98.7)	6189 (98.7)	9204 (98.7)	7068 (98.7)	9683 (98.7)	7099 (98.9)	10461 (99.0)	7405 (99.0)
	LDL-C	8032 (100.0)	6264 (99.9)	9324 (100.0)	7159 (100.0)	9806 (100.0)	7180 (100.0)	10561 (100.0)	7479 (99.9)
	HDL-C	8032 (100.0)	6265 (99.9)	9325 (100.0)	7160 (100.0)	9808 (100.0)	7180 (100.0)	10561 (100.0)	7481 (100.0)
	TG	8032 (100.0)	6266 (100.0)	9320 (99.9)	7160 (100.0)	9806 (100.0)	7179 (100.0)	10557 (99.9)	7479 (99.9)

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Supplementary Table 3. Average age of pCVD, pCHD and DM subjects in each year in each sex

Year		2008	2009	2010	2011
pCVD	Male	66.50	66.47	66.41	66.66
	Female	66.35	66.18	66.33	66.85
pCHD	Male	66.69	66.86	66.76	66.87
	Female	66.44	66.95	66.96	66.89
DM	Male	65.73	65.81	65.65	65.74
	Female	65.95	66.32	66.25	66.24

Supplementary Table 4. Percentages of the subjects who had been taking medicine for risk factors (%)

DrugBP: medication for hypertension; DrugLP: medication for dyslipidemia; DrugBS: medication for glycemic control.

A. pCVD

Year		2008	2009	2010	2011
DrugBP	Male	73.5	65.5	66.4	68.8
	Female	74.0	60.7	61.5	64.9
DrugLP	Male	21.5	23.6	26.3	29.3
	Female	33.2	34.8	36.5	39.7
DrugBS	Male	12.0	12.8	14.2	15.7
	Female	7.0	8.9	8.9	10.1

B. pCHD

Year		2008	2009	2010	2011
DrugBP	Male	57.2	59.0	60.5	61.8
	Female	54.3	55.6	56.6	58.0
DrugLP	Male	25.5	28.2	32.6	34.7
	Female	35.1	36.4	38.7	40.9
DrugBS	Male	17.2	14.0	14.4	15.2
	Female	10.8	8.2	8.5	8.4

C. DM

Year		2008	2009	2010	2011
DrugBP	Male	53.8	55.8	56.8	58.6
	Female	59.1	60.2	60.0	61.2
DrugLP	Male	27.3	29.9	32.5	34.3
	Female	45.4	48.7	49.7	52.7

Supplementary Table 5. Rates of the attainment of BP <130/80 mmHg in pCHD in each sex in each year (%)

P values of the time course change analysis of the attainment rate with the Cochran-Armitage test are also indicated.

Year	2008	2009	2010	2011	<i>p</i> value
Male	34.7	37.9	39.6	41.2	<0.001
Female	38.4	42.3	44.7	46.8	<0.001